REMARKS

I. Status of the Claims

Claims 1-3, 5-11, 13, 15-20, 23-46, 50-63, 66-72, 83-126 and 143-166 were pending in the April 27, 2010 Office Action. Claims 2, 3, 6-11, 13, 15, 19, 24, 30-32, 144-151, 165 and 166 were examined and rejected. Claims 1, 5, 16-18, 20, 23, 25-29, 33-46, 50-63, 66-72, 83-126, 143 and 152-164 are withdrawn. With this Reply, claims 2, 3, 6, 7, 9-11, and 30-32 are amended, claims 8, 15, 19, 24, 144-151, 165 and 166 are newly canceled, and claims 167-186 are newly added. The claim amendments, cancelations and additions are made without prejudice or disclaimer, and introduce no new matter. Claims 2, 3, 6, 7, 9-11, 13, 30-32, and 167-186 are presented for reconsideration.

II. Petition to Correct Priority Status

Applicants provide herewith, as Exhibit 2, a Petition to Accept Unintentionally Delayed Priority Claim Under 35 U.S.C. 120, as well as a specification amendment that updates the priority designation that was provided at the time of filing. Applicants request acceptance of the Petition, to correct the earliest priority designation to the filing of International Application No. PCT/IL01/01197 on December 24, 2001.

III. Rejections Under 35 U.S.C. § 112, First Paragraph - Enablement

Claims 2, 3, 6-13, 15, 19, 24, 30-32, 144-151, 165 and 166 are rejected under 35 U.S.C. 112, first paragraph, enablement requirement. The Office Action first concedes that the specification is enabling

> "for a method for the treatment of TNBS-induced-colitis in a first mouse in need of such treatment comprising: (1) orally administering to said first mouse colitis extracted proteins (CEP) prepared from colons that were removed from TNBS-induced-colitis mice, cut into small strips, mechanically homogenized, filtrated through a 40 mm nylon cell strainer, and the colitis extract supernatant separated from intact cells via centrifugation; (2) obtaining 0.5 x 10^6 liver associated lymphocytes and 2.5 x 10^6 splenocytes from a second mouse that had been treated with TNBS to induce colitis and had been orally administered CEP

> prepared as in step (1); (3) adding to a culture of the 0.5 x 10^6 liver associated lymphocytes and 2.5 x 10^6 splenocytes from step (2) antigen presenting cells and CEP prepared as in step (1); (4) optionally adding to said culture IL4, IL10, TGFβ ,IL18 or IL15, (5) administering the cultured cells of step (3) to the first mouse in need of such treatment to modulate the Th1/Th2 balance toward anti-inflammatory cytokine producing cells, resulting in an increase in the qualitative ratio between any one of IL4 and IL10 to IFNγ ***does not reasonably provide enablement for*** a method for the treatment of ***any*** immune-related or immune-mediated disorders or diseases in ***any*** mammalian subject in need of such treatment, by manipulating ***any or all*** NKT cell population(s) of said subject wherein manipulation of said NKT cell population(s) results in modulation of the Th1/Th2 cell balance toward anti-inflammatory cytokine producing cells, said modulation being mediated by ***any*** components, cells, tissues or organs of said subject's or another subject's immune system...."

pp. 2-3 of April 27, 2010 Office Action, emphasis in original.

Applicants traverse, first noting that the instant claims as amended are narrower than indicated in the above discussion, *e.g.*

> A method for the treatment of immune-related or immune-mediated disorders or diseases in a mammalian subject in need of such treatment, ~~by~~ the method comprising manipulating the NKT cell population of said subject, wherein manipulation of said NKT cell population results in modulation of the Th1/Th2 cell balance toward anti-inflammatory cytokine producing cells, said modulation being mediated by proteins extracted from tissue affected by the immune-related disorder, or at least one liver-associated cell of tolerized or non-tolerized subjects suffering from said immune-related or immune-mediated disorder or of said subject.

Claim 3. In this regard it is noted that each claim recites that the antigens related to said immune-related disorder are "proteins extracted from tissue affected by the immune-related disorder." Such a protein extract, exemplified by the "colitis extracted proteins" (CEP) were effectively utilized in the examples, e.g., Example 7 (pp. 79-86), where "culturing NK1.1+ T cells in the presence of disease associated antigens (subgroup E"5) leads to cytokine pattern that is similar to that of tolerized cells as manifested by increase IL10 secretion." (Specification, p. 81, bottom). It is further noted in this regard that the claims as amended do not recite "resulting in an increase in the quantitative ratio between any one of IL4 and IL10 to IFNγ," but do recite that the Th1/Th2 cell balance is modulated toward an anti-inflammatory response. While an

increase in the quantitative ratio between any one of IL4 and IL10 to IFNγ is one way of measuring the effectiveness of the NK1.1+ education process, the effectiveness of that process, *i.e.*, the modulation of the Th1/Th2 cell balance toward anti-inflammatory cytokine producing cells, can also be measured by evaluating the absolute measurement of IL4 and IL10 vs. IFNγ, for example as discussed in Example 7, *e.g.*, at page 81: "*ex vivo* education was examined by measuring secretion of IL10 (as compared to IFNγ secretion) by the different treated cells."

The Office Action also asserts that the claims are not enabled because Applicants do not know what particular component of the CEP affected the NK T cells. In response, Applicants first note that there is no requirement under 35 U.S.C. 112, first paragraph, that the applicant must know the precise mechanism of how an invention works. All that is necessary is that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." MPEP 2164.01(b). In the present case, Applicants assert that knowledge of the particular CEP component that affects the NKT cells is not necessary, because the skilled artisan would understand that "proteins extracted from tissue affected by the immune-related disorder" as claimed would be effective. As such, given the success of the CEP in educating the NKT cells in the exemplified inflammatory bowel disease case, the skilled artisan would understand that tissue affected by any other immune-related disorder likely has proteins that, when extracted from the tissue, would educate NK T cells *ex vivo* that, when reintroduced into the subject, would modulate the Th1/Th2 cell balance toward anti-inflammatory cytokine producing cells. Additionally, such a treatment could be tested with any particular immune-related disorder without undue experimentation by using the methods analogous to those described in the instant specification.

The Office Action additionally asserts, at page 6, that the skilled artisan would expect that methods of extracting proteins other than the method described in the specification "would be expected by the skilled artisan to have a materially different

composition from an extract prepared by the steps disclosed on page 42, 3rd paragraph of the instant specification...." In response, Applicants note that the Office Action does not provide any support for this assertion, as required ("examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure" – MPEP 2164.04). Furthermore, the skilled artisan would understand that the procedure disclosed on page 61, 3rd paragraph would allow the skilled artisan to practice the invention as claimed, and that other extraction procedures, *e.g.*, a detergent extraction as posited in the Office Action, could be tested without undue experimentation. The skilled artisan would also understand that there would likely be a number of extraction procedures that would obtain proteins that are useful for the present invention. Thus, the specification provides adequate guidance for the skilled artisan to practice the invention without undue experimentation.

In another aspect of the rejection, the Office Action asserts at p. 7-9 that NKT cells are generally unpredictable in their responses to antigens. The Action cites Ilan, Clin. Exper. Immunol., 2009, 158:300-307 ("Ilan, 2009"), in asserting that there was uncertainty in the art as to what controls the *in vivo* pro- or anti-inflammatory activities of NKT cells after Applicant's invention date. In response, Applicants note that the information described in Ilan, 2009 was not known at the time of filing, and the citation of this reference is not proper to assert non-enablement. See, e.g., MPEP 2164.05(a):

> In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977).

In the present case, the skilled artisan would not have understood the plasticity of NKT cells as described in Ilan 2009 at the time of filing. Further, such plasticity, which would presumably apply to murine as well as human NKT cells, did not affect the effectiveness of: (a) the oral treatment with the colitis extracted proteins (CEP) to treat colitis, as described in Example 1 at pp. 68-70 of the specification; (b) the *ex vivo* treatment of NKT cells to treat colitis, as described in Example 7 at pp. 79-86 of the specification; or

(c) the oral treatment with liver extract to treat con-A-induced hepatitis in Example 6 at pp. 104-106 of the specification. Thus, given the results achieved as described in the instant application, the skilled artisan, would understand that the described plasticity of NKT cells would not affect the effectiveness of the claimed methods. As noted above, however, the skilled artisan at the time of filing, would nonetheless have not known of the NKT cell plasticity as described ***eight years*** after the filing date.

In an additional aspect of the rejection, the Office Action asserts at p. 9-11 that results from murine NK1.1 T cells cannot be extrapolated to human CD56+ NK T cells. To support this assertion, the Office Action notes various differences between mouse and human NK T cells, including differences in frequency of NK T cells having various markers in liver and peripheral blood, as well as differences in cytokine production, and concludes that "the skilled artisan would consider extrapolating results from murine NK 1.1+ T cells to human CD56+ NK T cells an unpredictable endeavor."

In response, Applicants assert that the essential similarities between human and mouse NK T cells for the purposes of the present invention outweigh the differences, such that the skilled artisan would believe that the mouse model utilized in the Examples is sufficiently predictive of human results such that the claimed methods would be expected to be effective in humans. To support this assertion, Applicants point to Galli et al., 2003, Vaccine 21:S2/48-S2/54, provided herewith as Exhibit 3. At page S2/48 (the first page), Galli et al. note that both mouse and human NKT cells recognize CD1d and react to α-GalCer. The study described therein also found that mouse and human NKT cells were similar in their interaction with B cells. See, e.g., page S2/53, last paragraph.

Applicants also point to Wilson and Van Kaer, 2003, Curr. Pharm. Des. 9:201-20 (abstract provided herewith as Exhibit 4). That abstract describes numerous studies in mice directed to therapeutic intervention in autoimmune diseases, and concludes that "these studies provide a solid foundation for the development of NKT cell ligands as pharmacological agents for treatment of autoimmune diseases." This establishes that, at the time of filing, the similarities between NKT cells in humans and mice clearly

outweighed the differences between them, such that mice were considered a good model for studies of the type that lead to the instant invention.

The Office Action, at pp. 11-12, additionally cite three references, Margalit et al., (2006, Am. J. Gastroenterol. 101:561-8); Pozzilli et al. (2000, Diabetologia 43:1000-1004); and Wiendl et al. (2002, BioDrugs 16:183-200) to support the assertion that induction of tolerance by oral administration of antigens is unpredictable. In response, Applicants note that neither Margalit et al. nor Wiendl et al. were known at the time of filing (priority date December 24, 2001), and their teachings therefore cannot be cited as evidence for non-enablement. See MPEP 2164.05(a), discussed above. Further, Pozzilli et al., in teaching that oral administration of insulin to type 1 diabetics did not affect insulin autoimmunity, would not indicate anything to the skilled artisan about the effectiveness of "proteins extracted from tissue affected by the immune-related disorder," **as claimed**, in oral tolerization. Certainly, the success of the use of tissue extracts in (a) the oral tolerization to colitis, as described in Example 1 at pp. 68-70, and (b) to hepatitis, as described in Example 6 at pp. 104-106, would have given the skilled artisan **at the time of filing** the understanding that the **claimed** methods were enabled much more than a reference discussing oral tolerization with a different antigen than claimed, or two references that were not published at the time of filing.

In light of the claim amendments and the above discussion, withdrawal of the enablement rejection under 35 U.S.C. 112, is respectfully requested.

IV. Rejections under 35 U.S.C. § 102

Claims 2, 36-11, 13, 15, 19, 32, 144-151, 165 and 166 are rejected under 32 U.S.C. 102(b) as being unpatentable over Ilan et al. (WO 02051986). Although Applicants previously pointed to the priority designation of the instant application to argue that Ilan et al. is not prior art, the Office Action indicated that the priority designation was not proper, nor recognized by the Patent Office. To rectify this, Applicants provide (a) a specification amendment amending the priority designation provided in the specification as filed, and (b) a Petition to Accept Unintentionally

Delayed Priority Claim Under 35 U.S.C. 120. With the acceptance of the Petition, the earliest priority date is December 24, 2001, before Ilan et al. As such, Ilan et al. is not prior art under 35 U.S.C. 102(b) to the instant application. Withdrawal of the rejection under 35 U.S.C. 102(b) is therefore respectfully requested.

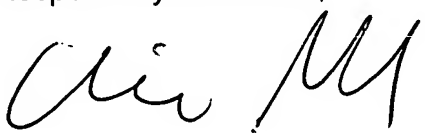
V. Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of the rejections of record and passage of all claims to allowance.

The United States Patent and Trademark Office is hereby authorized to charge all fees due herewith, including the fee for the Extension of Time (Three Months) request, and the fee for the Petition to Accept Unintentionally Delayed Priority Claim Under 35 U.S.C. 120, to Deposit Account No. 05-1135.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,



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